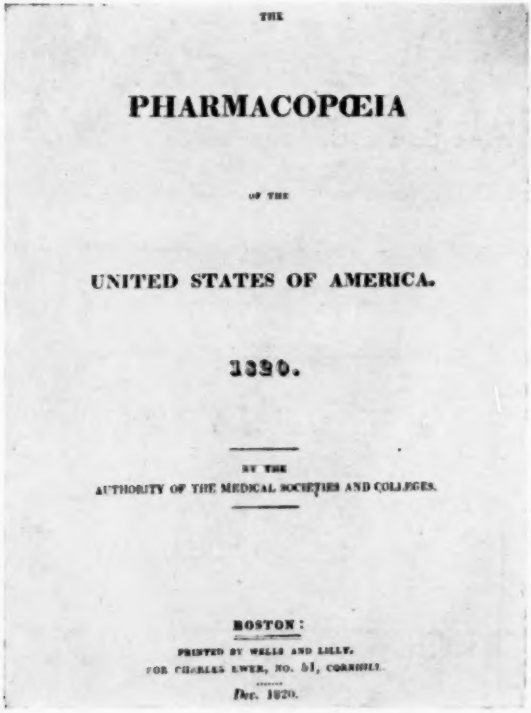
AMERICAN JOURNAL OF PHARMACY VOL. 123 SEPTEMBER 1951 NO 9

American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH



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OF THE

UNITED STATES OF AMERICA.

1820.

BY THE
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BOSTON:
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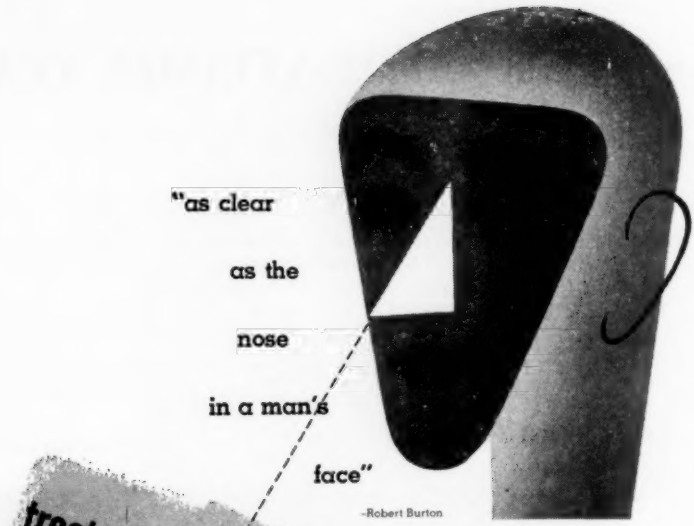

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EDITORIAL

EXTENDING THE USEFULNESS OF THE PHARMACOPEIA

ONE of the many projects which is being undertaken by the newly elected officers of the United States Pharmacopoeial Convention is extending the usefulness of the book itself to the practicing pharmacist and physician.

No one can argue that the Pharmacopeia is of no value to the health professions, for without the established standards of purity and strength set forth in both the Pharmacopeia and National Formulary the practice of medicine would fall into chaos. Actually, some standards must be available; the question is by whom shall they be written. Few indeed, would prefer to see our democratic system for preparing official standards give way to the only other alternative, namely, governmental decree based on the opinion of the F. D. A. alone. It is even unlikely that the Food and Drug Administration would relish the gigantic task of establishing drug standards. Furthermore, the use of official standards set by others makes their enforcement far easier in court. Americans would rebel were the "law", so to speak, written by the prosecution and quite admittedly it would be an unwholesome proposition.

So it is that every pharmacist, physician or drug manufacturer who buys the official books is actually contributing directly to the establishing of standards without which he could not function. This in itself is something worth far more to each practitioner than the cost of the two official compendia. It should also be remembered that, with the exception of two full-time officials, all of the work of revision, involving hundreds of thousands of man hours, is contributed without compensation by the Committee of Revision and the Board of Trustees. Were these scientists paid for their time the cost of the Pharmacopeia would be many times its present price. A similar situation obtains in the work of preparing the National Formulary by those on the National Formulary Committee.

In recent years some criticism has been directed particularly at the Pharmacopeia for its lack of practical usefulness in the day to

day work of both the pharmacist and physician. The officers of the Convention have not been unmindful of this sentiment and both Dr. Robert L. Swain, Chairman of the Board of Trustees, and Dr. Lloyd C. Miller, Director of Revision, have initiated a close study of ways and means to make the Pharmacopeia more generally useful. An advisory panel has studied this question and many suggestions are now being carefully investigated to see if they can be integrated into the framework of the Pharmacopeial text.

Such suggestions have been made as a table correlating official drugs with proprietary names, the inclusion of statements on pharmacologic action in the monograph and more dosage information including maximum safe dose. A number of pharmaceutical organizations have been asked to submit recommendations for consideration.

This program is excellent evidence of the sense of responsibility which those who are in charge of the Pharmacopeia feel towards the pharmacists and physicians of the country. The Pharmacopeia is an integral part of the system of medical care in this country; a system in which each pharmacist and physician is essentially free to practice with a minimum of governmental regimentation and restraint.

The Pharmacopeia deserves the support of every person and organization in the public health field. It is their organization, elected by delegates from every recognized body with an interest in public health. The Pharmacopeia, today, by the action and program of its officers gives every evidence of being aware of the necessity of meeting the challenge of changing conditions. No better guarantee exists that the Pharmacopeia will continue to merit and receive the endorsement of both the public and the professions which it has enjoyed for many decades.

L. F. Tice

MECHANISM OF THE LIBERATION OF HISTAMINE FROM CELLS

By Joseph W. E. Harrisson, Julian L. Ambrus and Clara M. Ambrus *

Introduction

MANY pathological conditions are thought to be related to the liberation of histamine from tissues. Such conclusions are based either on the demonstration of increased amounts of histamine in blood or tissues or on the therapeutic effect of antihistamine agents. Research of this nature was strongly intensified by the recent interest in antihistamine agents. For example, Troescher-Elam, Ancona and Kerr (1) found that histamine appears in the nasal secretions of patients with common cold. On this basis, antihistamines were tested and subsequently recommended as antidotes for common cold. (This question was discussed by Ambrus, Ambrus and Harrisson (2). There are, however, two factors which indicate that we must regard such data with some degree of concern.

(a) The effectiveness of antihistamines does not necessarily allow us to conclude that the condition alleviated by them is due to the liberation of histamine. Antihistamines possess a number of pharmacological actions which have no relation to their antihistaminic activity. For example, they exert a hypnotic and local anesthetic action (which may contribute to their anti-pruritic effect), they decrease muscular rigidity, and some of them depress motion sickness, etc.

(b) Increased histamine levels in organs and blood has been usually demonstrated by extracting histamine by specific methods (Code (3)) and testing by biological or colorimetric procedures. However, most of the extraction methods split off histamine from complexes. It is entirely probable that histamine is normally present in cells in protein-bound or other complex forms. In these states, it is probably pharmacologically inactive. Different pathological conditions as well as drugs probably lib-

* LaWall Memorial Laboratory of Pharmacology and Biochemistry, Philadelphia College of Pharmacy and Science.

erate histamine from these complexes yielding an active form. Moreover, since the extraction methods determine the total histamine content rather than the active histamine, some of the conclusions drawn on the basis of such methods may be misleading. Code and MacDonald (4) and Rose (5) demonstrated such a high histamine content in the blood of leukemic patients that intravenous injection of similar quantities into healthy persons would result in immediate shock and death. Yet the leukemic patients were apparently not in shock. It seems probable that in these cases the increased histamine content is explained by an increase of the bound, inactive form.

The number of factors which liberate histamine into an active form are without doubt numerous. It is probably sufficient to mention as examples: anaphylaxis and allergic phenomena (Dragstedt (6) and Rose (5); adrenaline (Staub (7), Koch and Szerb (8)); and curare (Grob, Lilienthal and Harvey (9)). The question which concerns us presently is rather the mechanism whereby such factors may liberate histamine from its bound state.

Mechanism of the Liberation of Histamine from Cells

Some agents and conditions have been mentioned which cause liberation of histamine. Little is known, however, about the mechanism of these procedures. Many of these factors increase cellular permeability or are directly injurious to cellular membranes. It is not likely, however, that histamine is present in the cells in a freely diffusible form and that a simple injury to the membranes would allow it to diffuse out. Feldberg and Kellaway (10) showed that if the dog's liver is perfused with staphylococcus toxin, a large amount of finely granulated cellular debris is liberated into the perfusate. The perfusate, however, has no significant histamine-like activity; histamine apparently is retained in an inactive form in the granules. If, however, the granules are coagulated by heating, active histamine appears in the supernatant fluid.

It would appear that drugs which cause the liberation of free or active histamine liberate histamine from protein or other complexes, thus proteolytic or related enzymes may be involved in such procedures. The proteolytic enzymes, trypsin and papain, are known to cause liberation of histamine. Snake and bee venoms may liberate

histamine because of the formation of lysolecithin (Feldberg, Holden and Kellaway (11, 12, 12a), Trethewie (13)) and also because they contain trypsin-like substances (Roche E Silva (14, 15)). Lewis (16) and Dale (19) postulated that protein breakdown may lead to the formation of peptone which could be responsible for the liberation of histamine.

The question of most interest is, of course, the liberation of histamine in anaphylactic shock and allergies. Kopeloff, Kopeloff, Zwemer and Kinsell (18, 19) have shown that a decrease of blood platelets parallels the degree of anaphylaxis in monkeys and rabbits. Since the platelets of rabbits are extremely rich in histamine, they assumed that histamine is liberated from the destroyed platelets. It is a question whether this mechanism is also true for other species, since the platelets of many species are not as rich in histamine as those of the rabbit, and since it has been shown that most of the liberated histamine originates from certain organs (e.g., from the liver in dogs and from the lungs in guinea pigs). Roche E Silva and associates (20, 20a, 21) studied this question and reported their results in a series of papers. They observed that from the perfused liver of sensitized dogs, no histamine is liberated by adding the antigen or peptone to the perfusion fluid if Tyrode solution or citrated blood was used as perfusing medium. If, however, the liver was perfused by whole blood, coagulation being prevented by the use of paraffin or silicone coated containers; large amounts of histamine and heparin were liberated from the liver. During this procedure aggregation and disintegration of platelets and leukocytes occurred. They concluded that the formation of aggregates and subsequent disintegration of leukocytes and platelets is associated with liberation of histamine in canine anaphylaxis. However, histamine liberation from these elements themselves may play only a minor role, since their histamine content is too small to account for the quantity of histamine made available. The fact that the histamine content of the liver decreases during anaphylactic shock has long been known. Therefore, Roche, *et al.*, postulated that an intermediate substance, liberated during platelet and leukocyte disintegration, may cause liberation of histamine from the liver. The same authors (22, 23) demonstrated that during anaphylactic shock the fibrinolytic activity of plasma increases. They assumed that a protease present in plasma is bound to an inhibitor, which during anaphylactic shock is liberated and activated, probably

by a kinase originating from disintegrating platelets and leukocytes. Similar activation of proteolytic enzymes by antigen and peptone had been demonstrated by Ungar (24) in guinea pigs. It is entirely probable that such a proteolytic enzyme would cause the liberation of histamine from the so-called shock organs (liver in the dog, lung in the guinea pig).

Summary

Many pathological symptoms are attributed to the liberation of histamine. Such conclusions have been based either on the demonstration of increased amounts of histamine in blood and organs or on the salutary effect of antihistamine drugs. The validity of such conclusions are doubtful as most of the histamine extraction methods determine active as well as inactive (bound) histamine. Furthermore, antihistamines may act also through mechanisms other than the antagonism toward histamine. One must consider the part that is played both by bound (inactive) as well as free (active) histamine.

Theories on the mechanism of histamine liberation by certain substances and anaphylactic phenomena have been briefly reviewed, and mention made of the theory of Roche E Silva and associates. According to these authors, peptone and anaphylaxis cause disintegration of platelets and leukocytes from which a kinase is liberated. This in turn liberates and activates a plasma protease bound normally to an inhibitor. This protease subsequently liberates histamine from its protein bound, inactive form in the shock organs.

At present the assumptions of Silva, *et al.*, appear most likely to be valid although the relationship to certain pathologic states is obscure.

Acknowledgment

The authors acknowledge with appreciation the assistance of Charles E. Moser ** and Charles A. Leonard who reviewed much of the literature in preparation for a research project.

** Fellow; Oak Ridge Institute of Nuclear Studies, U. S. Atomic Energy Commission.

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THE PROBLEM OF CHEMICALS IN FOODS *

By Kenneth E. Mulford **

IT is a pleasure to participate on such a distinguished panel before the American Bar Association. I am grateful for this occasion because I am returning to old friends for a discussion of mutual problems. My background is in law, although in recent years I have shifted to a management position in the Industrial Chemicals Department of our Company.

In the brief time at my disposal I should like to explore with you some of the practical problems involved in the chemicals-in-food question—from the standpoint and experience of a chemical manufacturer who has had close association with the Food Industry.

At the outset, perhaps it would be best to set forth a few salient facts to give perspective to the over-all problem.

In the first place, it is well to remember that all foods, as they occur naturally, are mixtures of complex chemical compounds. For example, we would need the space of a good-sized blackboard to list the various chemical formulae contained in an apple.

The second point to remember is that food preparations, even of the simplest type, involve complex chemical reactions. Take, for instance, the practice of smoking meat or fish, an art that has come down through the ages. The smoke of slow-burning hardwoods contains a host of chemicals, such as formaldehyde, acetaldehyde, acetone, phenol, acetic acid, methyl and ethyl alcohols and others.

Third, the use of chemical aids in foods is no new phenomenon. It was a well established practice while food preparation was still largely a home function. Grandma's pantry shelf contained such chemical improvers as: sodium aluminum sulfate, which is simply alum used to harden pickles and in baking powder; calcium acid phosphate, another baking powder ingredient, and sodium bicarbonate, usually called baking soda—as well as such old timers as sodium

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* Read before the Food, Drug and Cosmetic Division, American Bar Association, New York City, September 20, 1951.

** General Manager, Industrial Chemicals Division, Atlas Powder Company.

chloride, our common table salt; acetic acid, a major component of vinegar, and potassium acid tartrate, generally known as cream of tartar. It is interesting to note that the famous "Fanny Farmer Cook Book," which was first published in 1896, contains a quotation from Ruskin, reading in part, "It (cookery) means the economy of your Grandmothers and the science of the modern chemist."

Fourth, food production and preparation has moved from the home to industry, in order to meet the demands of our growing industrial society and population centers. The development of the food industry provided us with the benefits of mass production, processing and distribution. In the course of this transition, the food industry found that, in addition to the chemicals in grandma's pantry, it needed many other items developed by the chemical industry.

And fifth, the combined efforts of the food and chemical industries have been of tremendous benefit to the American consumer. Chemical aids in foods have come to serve a two-fold purpose: to increase the availability of foods by combatting pests and reducing spoilage; and to improve the nutritive value, keeping qualities, palatability, texture, and ease of preparation of foods. Result—the American family has the world's greatest supply of good, wholesome, enjoyable foods.

The current discussion of the chemicals-in-food problem must be viewed against this background of historic usage and accomplishment.

During the past year the Delaney Committee, which Mr. Kleinfeld so ably serves as counsel, has been studying the chemicals-in-food question, primarily with a view to determining whether present laws on this subject are still adequate.

Certainly no one questions the right and responsibility of Government to protect the health of our people. Industry shares equally in that vital job, and the Delaney Committee hearings reflect the high sense of responsibility by both chemical manufacturers and food processors in that regard. The record is one of accomplishment and of gains by the American People. It certainly justifies the thought that this is not an emergency matter, and there is time to weigh carefully all the implications of proposals for new legislation.

In commenting on the testimony before it, the Committee—in my opinion, very wisely—cautioned against placing "unnecessary

obstacles to technological improvements in food processing and production." This point deserves thorough consideration, for it is a major practical problem.

Some witnesses before the Delaney group have suggested that Congress give consideration to amending the Federal Food, Drug and Cosmetic Act to require that any chemical ingredient must be approved by FDA as to safety before it is used in any food product.

The Food and Drug Administration has submitted a tentative draft of such a "prior approval" amendment. The Manufacturing Chemists Association has brought forth a somewhat different approach. Other suggestions have been made. I do not intend to discuss the intricate legal aspects of any of the specific proposals—but, instead, to point out certain factors inherent in the basic idea of "prior approval."

As I see it, such a discussion involves consideration of three general, but closely inter-related, aspects of the subject—first, proof of safety; second, the levels and methods of usage factor, and third, the issue of technological usefulness.

At the core of various "prior approval" suggestions is the belief, in certain quarters, that there is need for regulation or statutory control of pre-testing chemical activities to establish safety.

Certainly, no right-thinking individual can quarrel with the principle of testing new food ingredients prior to public usage. All firms recognize that their fate is dependent on consumer protection. These points are axiomatic. Therefore, it would seem to be a simple matter to reach agreement on a legal requirement for pre-testing. Actually, however, it is exceedingly complex.

Getting right down to it, what do the words, "proof of safety" and "adequate testing," really mean?

Nothing is safe under all possible conditions of exposure or use. Despite this, some have held that no new chemical should be added to food until it has been proved in advance to be completely harmless or safe for continuous use over the human life span.

If the advocates of such a viewpoint are using these terms in the absolute sense, without taking into consideration that safety is a relative matter, then the comments of Dr. Bernard L. Oser, Director of the Food Research Laboratories, Long Island City, N. Y. are pertinent. Speaking before the annual meeting of the Institute of Food Technologists in June of this year, Dr. Oser said:

> "The standards of safety implied in these statements are unrealistic because they are humanly and scientifically impossible to comply with . . . Such ultimate proof of safety demands knowledge of all possible deleterious effects . . . The day is not in sight when such proof will be possible. Furthermore, how could one logically justify requiring it only on behalf of new chemicals, but not for all chemicals or for foods themselves, for that matter?"

It is obvious, therefore, that to make an affirmative showing that a material is "safe" would be extremely difficult, if not impossible. In a lawyer's terminology, it would be like being asked to prove a negative—that under every foreseeable circumstance, no possible harm can be caused. Common everyday foods may be "safe" for some people and not for others. Questions relating to the safety of any material can be asked *ad infinitum.*

The criteria of safety established for new products must be related to the criteria used for other accepted, generally similar products. (This is not a new idea, incidentally. It was suggested in the 1914 Department of Agriculture Report pertaining to the famed Remsen Board, appointed to study the use of what were then certain new chemicals in baking powder. The Report stated, "Alum baking powders are no more harmful than any other baking powders. . . .".)

Furthermore, determinations of safety or lack of safety must be made in the light of levels and methods of contemplated usage. This is the second point I wish to discuss.

Eminent scientists tell us that virtually all substances, when consumed in sufficiently large quantities, are toxic—i. e., they produce harm. Considerations as to levels and methods of usage, therefore, may well be the heart of the "pre-testing" problem, although frequently they seem to be overlooked in public discussions.

Actually, when a chemical manufacturer develops a new chemical, it is impossible for him to forsee all the potential uses for his product. Many times he has no idea that it might be found useful in foods. It is only after researchers in the food industry investigate and find the chemical useful in foods that we can move ahead to a solid toxicological testing program. Not until then will we have the clue to the all-important elements of manner and levels of use.

Since it is the finished food which is marketed to consumers, the primary responsibility for safety rests with the food manufacturer.

Nonetheless, the chemical manufacturer is deeply cognizant of his obligations, moral or otherwise, to provide the processor with a good, non-harmful product. In practical effect, what generally has occurred is a joint venture by food and chemical companies to make certain that food for the American consumer is safe.

Parenthetically, I might comment that I sometimes wonder, in light of these practicalities, why it is that certain proposals for "prior approval" legislation impose the burden of proof of safety solely upon the chemical manufacturer.

Both chemical and food manufacturers, of course, rely upon competent scientists to develop the toxicological evidence needed to sustain harmlessness. However, when one group of reputable scientists views data as sufficient and another group of equally able men tends to discount this work as insufficient, who is to resolve the scientific controversy and outline the right path? This is the kind of dilemma confronting Industry in the absence of generally accepted testing criteria.

In trying to analyze this problem in our own company we have come to the conclusion that an advisory panel of qualified scientists—perhaps modeled after the Food Protection Committee of the National Research Council—could be most helpful in assisting Industry and the Food and Drug Administration in determining the type and extent of tests to be performed. We have made this suggestion to the Delaney Committee and other interested groups.

My final area of discussion concerns technological usefulness. By this I mean the relative usefulness of the chemical in improving the food itself as well as its production and processing. This, too, is an important consideration, for recently the thought has been advanced that the technological usefulness of a proposed additive to food must be fully established before the safety issue is considered.

The immediate question arises: Assuming the food product is in compliance with existing law regarding adulteration and misbranding, who is finally to decide whether the new additive serves a proper function—a government agency, a public advisory group, industry or the consumer?

In actual fact, it is the food technologist who initially finds that a new chemical has some usefulness in food. However, neither the technologist nor the food manufacturer can ever be certain that the food product containing the chemical is really useful until it is subjected to the ultimate test—consumer acceptance.

Writing in the Department of Agriculture Yearbook for 1950-1951, Dr. Callie Mae Coons significantly points out, "Determination of the usefulness of foods to consumers is a serious problem, sometimes costly for both processors and and consumers . . . Consumer acceptance implies more than mental response or stated preference . . . It denotes action, with an opportunity for rejection, which may take place in the market, at the testing time, or after a series of experiences in using the product."

In discussing the palatability, as an example, Dr. Coons emphasizes: "The crucial test is the response of the people who eat the food."

Would "prior approval" signify the possible denial of consumer freedom of choice because some Government body decides that a new chemical is not useful, without even considering safety? To reverse the coin, should not the safety hurdle be cleared first and the product allowed to stand or fall on public acceptance?

I dare say no one would be rash enough to suggest the chemicals-in-food issue can be adjudged in terms of black or white. It's the gray areas—the regions of human, subjective judgments—which cause complications and thwart definitive solutions.

On the one hand, we have the splendid record of industry and government in protecting the public interest under existing laws. On the other, there are well-intentioned and honorable men who are convinced that some changes in the law are required.

In view of this situation—and in summary—I should like to leave these thoughts for your consideration:

(1) The use of chemicals in foods is a very old practice. The chemical and food industries are cognizant of their responsibilities; their record has been good and of tremendous benefit to the American People.

(2) Suggestions for legislation to make mandatory "prior approval" of chemical aids in food give rise to very complex problems. The various implications of such suggestions should be studied carefully.

(3) Safety must be viewed as a relative matter. To be asked to prove complete safety is like being asked to prove an absolute negative. It is scientifically impossible.

(4) Safety considerations must be related to contemplated methods and levels of usage.

(5) Any increase in the authority of our regulatory bodies primarily should concern safety. Fundamentally, technological usefulness should be determined by consumer reaction.

Over the years Industry and Government together have maintained vigilant watch over the safety of our Nation's foods. With or without a new law, that vigilance will continue. If further regulation is needed, let us keep in mind the practicalities of the situation. Above all, let us not close the door to progress.

THE EFFECT OF pH ON THE LIQUEFACTION OF GELATIN MEDIUM BY STAPHYLOCOCCUS AUREUS

By Louis Gershenfeld and Eugene Micklin *

Introduction

GELATIN liquefaction has been used for many years as one of the criteria in identifying various bacterial species.

Levine and Carpenter (1) have reported the change in viscosity of gelatin medium. The viscosity of autoclaved gelatin (at 121° C. (15 lbs. pressure)), stored at 22° C., changed little for the first 2 or 3 days, after which there was a sharp increase for a week to 10 days. A gelatinolytic organism brought about rapid liquefaction when inoculated into the same medium 10 days to 2 weeks later. The latter occurs because more of the gel form must be transferred to the sol state to make liquefaction evident (1).

Berman and Rettger, as noted by the above authors, report that "the power of an organism to liquefy gelatin is not necessarily accompanied by the ability to decompose the gelatin and seize upon it as food" (1).

Another factor that may control gelatin liquefaction is the pH of the medium. It is known that in general, the activity of an enzyme depends on the hydrogen ion concentration. There exists a narrow zone of maximum activity, and on both sides of this zone the activity gradually decreases to zero (2). Buffers may exert specific actions on enzymes, or even substrates. It is also possible that the ordinary substrates may have a considerable buffer capacity (2).

Another point to consider is the different kinds of gelatin, which may liquefy at various temperatures. The general composition of gelatin is as follows (3):

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* Department of Bacteriology, Philadelphia College of Pharmacy and Science.

Approxmate Percentage Composition of Animal Protein-Gelatin.

Substance	Percentage Composition
Nitrogen	18.0
Sulfur	0.5
Arginine	9.2
Histidine	0.9
Lysine	5.3
Tyrosine	0.3
Tryptophane	0.0
Phenylalanine	2.4
Cystine	0-0.3
Methionine	1.1
Threonine	1.7
Serine	3.7
Leucine	3.6
Isoleucine	1.2
Valine	2.7
Glutamic Acid	11.6
Aspartic Acid	9.6
Glycine	26.6
Alanine	10.4
Proline	17.2
Hydroxyproline	15.0

The approximate amino acid composition of gelatin protein as given in another report is as follows:

	%
Alanine	11.2
Arginine	8.5
Aspartic Acid	9.6
Cystine	0-0.2
Glutamic Acid	6.1
Glycine	26.5
Histidine	1.1
Hydroxyproline	14.6
Isoleucine	1.9
Leucine	4.1
Lysine	4.8
Methionine	0.9
Phenylalanine	2.2

Substance	%
Proline	17.2
Serine	3.7
Threonine	1.7
Tryptophan	0.0
Valine	2.8

It has been reported that the presence of magnesium and calcium salts is necessary for the production of gelatinase. The former stimulates growth, and the latter actively stimulates the production of the enzyme (4), (5).

Many organisms which liquefy gelatin are unable to break it down further to free amino acids: *Staphylococcus aureus,* although liquefying gelatin, is unable to hydrolyze the protein to free amino acids and can probably neither assimilate nor oxidize this substance. Gelatin, digested by proteolytic organisms such as *Proteus vulgaris* is carried to the amino acid stage, and finally to the liberation of ammonia (4).

The optimum reaction for the proteinase activity of bacteria varies between pH 7.0 and 8.0 with the maximum activity at 7.2. The isoelectric point of gelatin is 4.4 to 5.6 (7); more specifically 4.80 to 4.85 (6). Gelatin from acid treated precursors has an isoelectric range of 7 to 8.

Purpose:

This presentation was conducted to determine the effect of pH on gelatin liquefaction by *Staphylococcus aureus.*

Experimental

Material:

Organism—The test organism used was a 48 hour culture of *Staphylococcus aureus.* This was obtained from a stock culture at the Philadelphia College of Pharmacy and Science, which had been isolated from the air. Using Bacto-Coagulase Plasma, the *Staphylococcus aureus* was found to be coagulase positive (8).

Media—Difco Nutrient Gelatin was used. The origin or source of the gelatin is not given on the label or in the Difco Manual. The formula is as follows (9):

Beef Extract	3 Gm.
Peptone	5 Gm.
Gelatin	120 Gm.
Water a sufficient quantity	

Distilled water (500 ml.) was added, making the gelatin medium double strength. This was warmed to 50°C. to dissolve all of the ingredients. The medium was sterilized at 121°C. (15 pounds pressure) for 15 minutes.

Buffer solutions—The following buffer solutions were prepared: Solutions of 0.2 M sodium monophosphate and 0.1 M citric acid were mixed in the proper proportions for pH values 3.4, 4.0, 4.4, 5.0, and 5.6 (10). Solutions of M/15 sodium monophosphate and M/15 potassium diphosphate were mixed in the proper proportions for pH values of 5.6, 6.0, 6.4, 7.0, 7.6, 8.0, and 8.4 (11). The prepared solutions were checked with a Beckman pH meter.

Viscosimeter—An Ostwald viscosimeter was used; it was cleaned with hot water, acetone, and dried with air by means of an air pump.

Procedure

Into each of 26 tubes, 5 cc. of gelatin medium and 5 cc. of pH buffer solution at the desired pH were added as follows:

# of Tubes	pH	Gelatin Used cc.	Buffer Sol'n Used cc.	
2	3.4	5	5	
2	4.0	5	5	
2	4.4	5	5	
2	5.0	5	5	
2	5.6	5	5	
2	5.6	5	5	
2	6.0	5	5	
2	6.4	5	5	
2	7.0	5	5	
2	7.6	5	5	
2	8.0	5	5	
2	8.4	5	5	
2	—	5	5	(dist. water)

Each solution was thoroughly mixed with a wooden applicator. The applicator was removed without touching the sides of the tube to prevent the non-absorbent plugs from sticking when the tubes were stoppered. The plugs for stoppering the tubes were non-absorbent cotton wrapped in a 1½ inch square silk cloth.

Two tubes for each pH value were prepared, one for inoculation with the organism and the other as the control. Each tube was labeled, stoppered, and autoclaved at 121° C (15 pounds pressure) for 15 minutes. They were allowed to cool at room temperature, after which they were placed in the incubator at 37° C. until the next day.

On the following day, the tubes were placed in a cold water bath at 5° C., for 10 minutes; this solidified the medium to facilitate inoculation. A straight sterile platinum wire inoculating needle was dipped into a 48 hour culture of *Staphylococcus aureus* and stabbed into each tube of gelatin medium containing the buffer solution for each pH value. The control tubes were not inoculated. All tubes were incubated for 5 days at 37° C.

After the required 5 day incubation period, the tubes were placed in a water-bath at 5° C. for 10 minutes. They were examined macroscopically for liquefaction of gelatin. (See Table 2).

An Ostwald viscosimeter was used to measure the viscosity of the medium after incubation. The instrument was cleaned with hot water, acetone, and dried with air by means of an air-pump. A glass cylinder tank was filled with warm water and lowered into a water-bath that remained at constant temperature. The water in the tank and water-bath were adjusted at 35° C.

The gelatin tubes were placed in the water-bath for a 15 minute period, so that they were at a uniform temperature. Four cc. of the contents in each tube were removed, and introduced by means of a pipette into the large neck of the viscosimeter. A rubber tube was fastened over the small opening of the instrument. The viscosimeter was placed in the tank and held by means of a burette clamp attached to a ring stand. By drawing air into the rubber tube, the upper meniscus of the medium was raised over the upper mark of the instrument. Then, the rubber hose was removed. As the upper meniscus of the medium passed the upper mark, the time was recorded by means of a stop-watch, and the latter was stopped as the meniscus passed the lower mark on the instrument. This was repeated with

every tube, each time cleaning the instrument and pipette as mentioned. The time periods were recorded (Table 2).

All inoculated tubes were examined for growth after 5 days' incubation. They were compared with their respective controls for turbidity. Tubes with a pH of less than 6.0 were difficult to compare, as the turbidity was extremely slight when compared to the controls. Therefore, a loopful of the liquefied gelatin medium was streaked from each inoculated tube on to a nutrient agar clant. The agar tubes were incubated for 24 hours at 37° C., and examined for growth (see Table 2).

The entire procedure was repeated as above, differing only in the temperature of incubation. These tubes were incubated at room temperature (21° C.) (see Table 3).

Findings

After the medium was prepared and sterilized, it was allowed to cool at room temperature (21° C.). The following was observed:

TABLE 1.

EFFECT OF pH ON STERILIZED GELATIN AT ROOM TEMPERATURE.

pH	Gelatin
3.4	L
4.0	L
5.0	L
5.6	S
5.6	S
6.0	S
6.4	S
7.0	S
7.6	S
8.0	S
8.4	S
(Water)	S

Liquid (L)
Solid (S)

Thirteen gelatin tubes were inoculated with the test organism as previously mentioned, and their respective control tubes were placed in the incubator for 5 days at 37° C. They were examined macroscopically. The viscosity was taken, and is recorded in table 2.

TABLE 2.

EFFECT OF pH ON GELATIN AFTER 5 DAYS' INCUBATION AT 37° C.

pH	Macroscopic Examination: Inoculated Tubes	Macroscopic Examination: Control Tubes	Viscosity Measurements at 35° C. in Min/Sec/O. 1 S.: Inoculated Tubes	Viscosity Measurements at 35° C. in Min/Sec/O. 1 S.: Control Tubes
3.4	Solid	P. Solid	5:24:8	5:10:8
4.0	"	Solid	6:16:3	6:06:6
4.4	"	"	7:08:4	6:38:8
5.0	"	"	8:14:8	8:03:6
5.6 Cit/K	"	"	9:14:3	9:45:2
5.6 K/Na	"	"	7:03:3	7:38:2
6.0	"	"	6:58:6	8:26:2
6.4	"	"	3:49:7	8:32:4
7.0	Liquid	"	2:53:5	11:02:0
7.6	"	"	3:15:0	10:02:5
8.0	"	"	3:30:8	11:56:5
8.4	"	"	3:29:6	7:24:6
(Water)	Solid	"	6:57:0	7:51:5

Viscosity in Relation to Distilled Water *	
Inoculated Tubes	Control Tubes
4.53	4.34
5.26	5.12
5.99	5.57
6.92	6.76
7.75	8.18 Cit/K
5.92	6.40 K/Na
5.85	7.07
3.21	7.16
2.42	9.25
2.72	8.42
2.94	10.02
2.93	6.21
5.83	6.59

$$\frac{\text{Viscous flow of medium}}{\text{Viscous flow of water}} = \text{Relative Viscosity}$$

* The average flow of distilled water through the viscosimeter was one minute, eleven and five-tenths seconds. This was used to determine the relative viscosities of the gelatin medium.

Table 3 records the findings in a similar series but in these the inoculated tubes were incubated at 21° C.

TABLE 3.

EFFECT OF pH ON GELATIN AFTER 5 DAYS' INCUBATION AT ROOM TEMPERATURE (21° C.).

pH		Macroscopic Examination At 5° C. Inoculated Tubes	Control Tubes	Viscosity Measurements at 35° C. in Min/Sec/O. 1 S. Inoculated Tubes	Control Tubes
3.4		P. Solid	P. Solid	4:51:6	4:35:8
4.0		" "	" "	5:42:4	5:36:6
4.4		Solid	Solid	6:35:3	6:07:4
5.0		"	"	7:19:4	6:58:6
5.6	Cit/K	"	"	8:34:4	8:05:8
5.6	K/Na	"	"	7:02:6	6:57:4
6.0		"	"	7:49:7	7:46:8
6.4		"	"	8:01:5	8:13:6
7.0		Liquid	"	7:06:4	8:49:6
7.6		"	"	4:37:5	8:32:9
8.0		"	"	3:53:8	9:54:8
8.4		"	"	3:43:2	9:02:2
(Water)		Solid	"	7:23:8	7:00:8

Viscosity in Relation to Distilled Water*		
Inoculated Tubes	Control Tubes	
4.07	3.71	
4.78	4.70	
5.52	5.13	
6.14	5.85	
7.19	6.79	Cit/K
6.79	5.83	K/Na
6.57	6.52	
6.73	6.90	
5.96	7.40	
3.88	7.17	
3.26	8.31	
3.12	7.58	
6.20	5.88	

* The average flow of distilled water through the viscosimeter was one minute, eleven and five-tenths seconds. This was used to determine the relative viscosities of the gelatin medium.

Table 1 indicates that the buffer solutions used have an effect on the state of the gelatin medium. Freshly prepared medium will remain liquid at low pH values, but at pH values of 5.0 and higher, the gelatin medium is solid as indicated in Table 2.

The inoculated tubes varied under these conditions. No liquefaction was observed macroscopically in any of the lower buffer gelatin tubes. At a pH of 7.0 to 8.4, gelatin liquefaction occurred. This was also indicated by the relative viscosities of the solutions. The lowest viscosity of the inoculated tubes was 2.42 at a pH of 7.0.

The greatest viscosity was at a pH of 5.6, where the composition of the buffer did have some effect on the gelatin. By using sodium monophosphate and citric acid as the buffer solution, the viscosity of the inoculated tube was 7.75. At the same pH value with a buffer solution consisting of sodium monophosphate, the viscosity of the inoculated tube was 5.92. The control tubes were approximately similar to the above, the former having a viscosity of 8.18, while the latter viscosity was 6.40.

The viscosities of the inoculated tubes and control tubes were approximately the same until a pH of 6.4 was attained. At pH values above 6.4, wide differences in the viscosities of the inoculated tubes and control tubes were observed. At a pH of 8.0, the control tube showed the greatest viscosity, 10.02 (least flow), while the inoculated tube had a very low viscosity, 2.94. This was the greatest difference observed between the pair of tubes. The results were unsatisfactory at a pH value higher than 8.0, as the difference between the inoculated tube and control was small.

The results obtained at room temperature (21° C.) were somewhat similar to the above, as indicated in table 3. Macroscopic observations at 5° C. were the same as in table 2, with the exception that the controls and inoculated tubes at pH values of 3.4 and 4.0 were partially solid.

Again, between a pH of 3.4 and 5.6, the inoculated and control tubes were approximately the same. No marked degree of change existed until a pH value of 7.0 was attained. The viscosity of the inoculated tube was 5.96, while that of the control tube was 7.40. This difference was small in comparison with the same pH tubes at a temperature of 37° C. Also, the greatest difference in viscosity between the inoculated tube and control tube was at a pH value of 8.0; the former was 3.26, while the latter was 8.31. Again, this difference was less then the similar tubes at a temperature of 37° C.

Summary

Tubes of gelatin medium were prepared with pH values varying from 3.4 to 8.4. The pH adjustments were made by the use of two buffer systems; a monophosphate-citric acid buffer mixture and a monobasic-dibasic phosphate buffer mixture. One set of buffered gelatin tubes was inoculated with a culture of *Staphylococcus aureus*. The other sets were used as controls. All tubes were incubated at a temperature of 37° C. for 5 days. At the end of this time, the tubes were examined for gelatin liquefaction at a temperature of 5° C. The flow of each tube was measured at 35° C., and the relative viscosities were determined.

The above was repeated, varying only the incubation temperature; this was room-temperature (21° C.).

Conclusions

Tubes of gelatin medium having a pH value of 7.0 or higher and at an incubation temperature of 37° C. are more satisfactory to indicate optimum liquefaction. A pH of 7.0 or 8.0 was ideal, as the control tubes at these pH values were solid at 5° C. Gelatin tubes at pH values of 7.0 or 8.0 showed a high viscosity at 35° C.; whereas the inoculated tubes were liquid at 5° C. and had a low viscosity at 35° C. At a pH value of 6.0 and lower, the inoculated tubes and control tubes were quite similar, indicating that these buffers are of little value in the preparation of gelatin medium to observe liquefaction.

Also, pH values above 8.0 are not acceptable, as the viscosities of the inoculated and control tubes tend to approach each other.

At room temperature, the results obtained indicated the differences between the inoculated and control tubes were not as great as that of 37° C. Therefore, the 37° C. temperature was best for noting gelatin liquefaction.

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SELECTED ABSTRACTS

A Follow-Up Report of Survivors of Tuberculosis Meningitis Treated With Streptomycin. Calnan, W. L., Rubie, J. and Mohun, A. F. *Brit. Med. J. No. 4710:*794 (1951). A follow-up of study of the 18 survivors of a group of 54 patients with tuberculous meningitis was reported by the authors. The observation period has been extended to 2½ to 3½ years. Two patients died during the intervening time and the survival rate has thus been reduced to 30 per cent. Three patients relapsed but recovered with further treatment with streptomycin. Two of the patients developed tubercular lesions which were non-meningeal and which responded to treatment.

Sequelae evident in the survivors were deafness in two children, a minimal hemiplegia in one child, retarded development in one, and an intellectual defect in one. All 14 of the survivors tested showed complete loss of vestibular response during caloric tests but none showed clinical ataxia in a good light. Audiograms showed a marked hearing loss in 2 but the remaining were normal.

Slight variations in the cerebrospinal fluid was observed up to 2 years after the cessation of treatment. Although no other evidences of activity of the disease were evident the authors felt that patients could not be definitely considered as cured even after 2½ years but that further observation was necessary.

The Use of Gallamine Triethiodide as an Adjunct to Electroplexy. Smith, R. H. F., and Thomas. D. L. C. *Brit. Med J. No. 4711:*860 (1951). The use of Gallamine Triethiodide (tridiethylaminoethoxy benzene triethyliodide) as a muscle relaxant was studied by the authors in patients requiring electroconvulsive therapy but in whom there were certain contraindications to such treatment, namely, severe rheumatoid arthritis and hypertension.

The drug was administered intravenously in doses of 60 to 100 mg. to 12 patients, two men and 10 women. Within 3 to 5 minutes complete paralysis of the flexor muscles of the forearm and of the

foot and leg occurred. The neck muscles failed early, in about 2 or 3 minutes. Complete relaxation of the abdominal muscles occurred in about 3 minutes. A rise in blood pressure occurred in many of the patients, but this was later traced to apprehension; for the injection of 0.25 Gm. of thiopentone sodium prior to the injection of the Gallamine triethiodide eliminated this effect.

When the convulsion was induced there was no effect of the drug evident to in any way impair the seizure. After the injection of the full dose of the drug recovery was rapid and was complete within 20 to 30 minutes. In two patients the paralysis was completely abolished within 10 to 15 minutes by the injection of 1 mg. of neostigmine.

The authors reported that there were no marked side effects. Slight areas of erythema with weal formation were noticed around the site of injection on several occasions. There was no bronchospasm after over 90 injections and there were no adverse effects on kidney function or blood picture. A mild cyanosis from temporary apnoea did occur in several cases.

Advances in the Diagnosis and Treatment of Adrenal Insufficiency. Thorn, G. W., Forsham, P. H., Frawley, T. F., Wilson, D. L., Renold, A. E., Frederickson, D. S., and Jenkins, D. *Am. J. Med. 10:*595 (1951). The authors summarized their experiences with ACTH and cortisone as tools for the diagnosis and treatment of adrenal cortical insufficiency. The specific stimulation of the adrenal cortex by the administration of ACTH has made possible a determination of the reserve capacity of the gland. Thus, it is no longer necessary to await the development of advanced disease before accurate diagnosis can be made. In the 4-hour ACTH test 25 mg. of ACTH is administered intramuscularly and the number of circulating eosinophils is followed as the measure of adrenal response. The maximum response, occurring 4 hours after stimulation, reflects the release of 11,17-oxysteroids from the stimulated cortex. In clinical trials the majority of normal subjects showed a drop of 70 per cent in circulating eosinophils four hours after stimulation as contrasted with an average drop of only 7 per cent in 50 Addisonian patients. Some of the latter even showed a rise in eosinophils. A more clear-cut demarcation between primary and secondary adrenocortical disease

may be obtained by use of the 48-hour ACTH test. An initial intramuscular injection of 25 mg. of ACTH is followed by 10 mg. every 6 hours for a total of 48 hours. This provides a longer period of stimulation and an opportunity for the activation of a cortex which is only involuted and not destroyed.

In the realm of therapy the authors pointed out that desoxycorticosterone acetate has potent salt and water retaining capacities but in the usual dosages employed has no effect on intermediary carbohydrate, fat and protein metabolism. Cortisone acetate has only about one-fiftieth the salt-retaining potency of desoxycorticosterone but does act to preserve carbohydrate stores by decreasing the utilization of carbohydrate and increasing that of fat. Thus, cortisone has filled a gap in therapy which has made it possible to restore many patients to an active life. The authors verified these conclusions with clinical experiences, as reported.

A Rapid Test for Germicidal Action. Buchbinder, L., and Zaretsky, P. *Am. J. Public Health 41*:537 (1951). When concentrations of 100 p. p. m. or greater of fast-acting germicides are added to suspensions of actively motile coliform organisms, practically instantaneous cessation of motion occurs. This phenomenon has been suggested as a rapid test for germicidal action. It has particular application to the field-testing of germicides in sanitation inspections and also in educational excursions.

The test is performed by mixing 1 cc. of bacterial suspension with 1 cc. of double the germicidal concentration to be tested in a test tube. A portion is transferred to a concave slide, covered with a cover slip and examined for motility under a microscope within 30 seconds. A control suspension is made by dilution with a buffer and examined in the same manner, concurrently. The dramatic cessation of motility with concentrations of 100 p. p. m. practically eliminates subjective bias in such tests. However, when lesser concentrations were used greater variation was obtained since the subjective evaluation of the results was based upon a gradual shading of reduced motility.

Quaternary ammonium and chlorine compounds were studied by the authors since these types of compounds are most frequently encountered in sanitary disinfection. The test was equally satisfactory with both types of compounds. A series of field tests were conducted

to test the presence of adequate germicidal concentrations in use-dilutions in eating establishments. They found fairly good correlation between the degree of motility test determined in the field and the per cent killed test carried out in the laboratory. As a rule the findings with these two tests were parallel but not identical.

The Use of Cortisone and Insulin in the Palliative Treatment of Rheumatoid Arthritis. Henderson, E., Gray, J. W., Weinberg, M., Merrick, E. Z., and Seneca, H. *J. Clin. Endocrinol. 11*:119 (1951). The authors object to the use of the term "physiologic" in reference to the treatment of rheumatoid arthritis with massive doses of cortisone. They feel that the rapid relief of pain, the sudden abatement of muscular spasm permitting flexibility of otherwise frozen joints, the euphoria, and the prompt return to the pretreatment status following cessation of therapy suggest a completely un-physiologic action. They suggested that the well-known glycogenic action of cortisone induces an extraordinary and pathologic synthesis of carbohydrate at the cellular surface-boundary. Thus noxious agents, such as the etiologic factor(s) responsible for rheumatoid arthritis, are confronted with cells rendered temporarily less destructible and they are unable to provoke inflammation.

The authors sought to determine whether or not the concurrent administration of insulin would provide more utilizable carbohydrate for the action of cortisone upon cellular structure. They have concluded, as a result of their studies, that insulin is a direct synergist to cortisone. They found that the administration of 50 mg. of cortisone with 20 to 60 units of insulin produced major improvement or complete remission in 11 of 12 patients with rheumatoid arthritis and minor improvement in the remaining patient. The experience was comparable in all respects, with the exception of side effects, with that obtained with 100 mg. doses of cortisone without insulin. Side effects were markedly reduced, in fact, the only side effects which occurred were infrequent and mild hypoglycemic episodes which were readily controlled. Maximal benefit was obtained after a treatment period varying from 10 to 30 days.

The authors suggested that further study may prove that this method of therapy may provide a safer and less expensive palliative

management of the disease. They emphasize, however, that the treatment is only palliative, for in their studies, although they have observed definite evidences of striking reversal of the disease process, they have only temporarily been able to obscure the clinical and laboratory evidence of the disease.

The Fungicidal Activity of Ethyl Vanillate. McVickar, D. L. The Society of American Bacteriologists, General Meeting Chicago, May 27-31, 1951. The search for a fungicidal substance which is active against the pathogenic fungi responsible for systemic mycotic infections and the accompanying high mortality rate, has brought forth some fruit. A new chemical, ethyl vanillate (ethyl-3-methoxy-4-hydroxybenzoate) has been found to be very effective against almost all of the pathogenic fungi. The only two pathogenic fungi against which this agent does not seem to be effective are, *Cryptococcus neoformans* and *Candida albicans.*

Ethyl vanillate is an inexpensive compound which is a by-product of the manufacture of wood pulp. It has been found to kill or inhibit the growth *in vitro* of all pathogenic fungi, except the two mentioned, at levels of 30 to 40 mg. per cent. The same levels in the human blood have been shown to be non-toxic. Particular concentrations *in vitro,* characteristic for each organism, caused the cessation of growth without being fungicidal. Higher concentrations were shown to be fungicidal and lower concentrations simply reduced the rate of growth in proportion to the concentration. There is also evidence to indicate that increasing the complexity of either the ester or the ether group in the molecule results in an increased fungicidal activity.

Reduced Dietary Requirements for Vitamins in Chicks in the Presence of Aureomycin. Biely, J. and March, B. *Science 114:*330 (1951). A number of reports have appeared with regard to the effect of aureomycin on the growth rate of chicks and other animals. In most animals, with the exception of the ruminants, the inclusion of an antibiotic in the ration resulted in an increased rate

of growth. However, conflicting reports have appeared. The authors stated that varying results were obtained in their laboratory in the response of chicks to the addition of aureomycin to the diet, probably due to differences in the composition of the diet.

A study was undertaken to determine the effect of aureomycin on the growth rate of chicks fed a ration deficient in one of the vitamins. The first series employed a folic acid-deficient ration which was fed to chicks with and without aureomycin. At 4 weeks of age the chicks not receiving aureomycin averaged 308 Gm. in weight and were poorly feathered. Those receiving aureomycin averaged 410 Gm. and were well feathered. It would thus appear that aureomycin in the diet of the chicks reduced the requirements for folic acid.

In another study a basal ration was fed with and without aureomycin. The addition of aureomycin had no effect upon the growth rate. However, when riboflavin, nicotinic acid, and folic acid, respectively, were eliminated from this ration there was a marked decrease in the growth rate. When aureomycin was added to each of these vitamin deficient diets the growth rate was increased to that obtained with the complete basal ration.

The authors suggested that the effect of aureomycin in lowering the dietary requirements for certain vitamins, is brought about through a reduction in the number of intestinal micro-organisms which might compete with the host for members of the vitamin B complex. It also might be that aureomycin would make possible the proliferation of micro-organisms which synthesize these vitamins *in vivo*. Thus, a larger proportion of the vitamins in the diet would be made available to the chick for absorption, or as a result of favorable biosynthesis.

Spermatogenic Rebound After Testosterone Propionate Therapy. Heckel, N. J., Rosso, W. A., and Kestel, L. *J. Clin. Endocrinol. 11*:235 (1951). Five healthy, normal, well-nourished men with a moderate oligospermia were given testosterone propionate by intramuscular injection at the rate of 50 mg. three times a week. This therapy was continued until spermatogenesis had decreased until a stage of azoospermia or near-azoospermia was reached. A total of 1500 mg. was required in one case, 1600 mg. in 2 cases, 2500 mg. in one case, and 2550 mg. in one case. Analyses of the seminal fluid

were made at 6 to 8 week intervals for as long as 29 weeks after treatment was discontinued. Testicular biopsies were performed on the 5 patients before treatment was started and on 3 of the patients about 20 weeks after treatment was terminated.

No extrinsic factor was found to explain the oligospermia present initially. The biopsies performed initially revealed spermatogenic arrest at various levels. The reduction of the sperm count during therapy had been shown previously to occur with testosterone therapy. Following the withdrawal of therapy there was a gradual increase in the spermatogenic activity in all five cases until the production of mature spermatozoa far exceeded the number found before treatment. The post-treatment biopsies obtained in 3 cases all showed an increase in the maturation processes.

The authors were not able to offer an explanation for the physiological changes brought about by the androgen therapy. It is not certain whether the initial depression of spermatogenic activity followed by marked improvement after therapy is discontinued may be caused by androgenic substances alone or whether other agents are capable of eliciting such responses.

Aureomycin Treatment of Acute Infectious Lymphocytosis. Malhotra, S. L. *Lancet 2*:202 (1951). Four cases were described in which the clinical signs and symptoms were so mild as to escape attention in the diagnosis of lymphocytosis. However, blood studies and a negative Paul-Bunnell reaction established the diagnosis as acute lymphocytosis and the circumstances gave evidence that the condition was infectious. The blood picture showed a well-marked leucocytosis with a relative and absolute preponderance of mature small lymphocytes. No abnormal cells were observed.

Aureomycin was administered orally in 3 cases with dramatic results. Clinical symptoms were reduced to near normal within 24 hours and the white blood cell counts returned to normal in about 5 days following the beginning of treatment. The one patient not given aureomycin was treated symptomatically but symptoms persisted for about 4 weeks and the lymphocytosis persisted for about 5 weeks from the onset of the disease. The incubation period in these cases was apparently 8 to 10 days.

The Use of Procaine Amide in the Treatment of Ectopic Rhythms. Berry, K., Garlett, E. L., Bellet, S., and Gefter, W. I. *Am. J. Med. 11:*431 (1951). Procaine amide differs from procaine in structural configuration in that the para-aminobenzoic acid and the diethylaminoethanol are bound together through an NH group rather than an ester linkage. This compound is not affected by the procaine esterase of the body and thus is effective by either the oral or intravenous route. The serum levels of procaine amide decrease only 10 to 15 per cent per hour following a single intravenous injection. Indirect evidence indicates that it acts by depressing the myocardium, as does quinidine.

Procaine amide was administered in 98 episodes of electrocardiographically proven arrhythmias in 78 patients. A return to normal sinus rhythm was accomplished in 61 of the episodes. The drug was given intravenously to 21 patients, intravenously until ectopic rhythm was abolished and then orally to 12 patients, and orally alone to 45 patients. The intravenous dose was given at a rate of not more than 200 mg. per minute under constant electrocardiographic control until there was a return to normal sinus rhythm, until toxic symptoms were observed, or until a total of 1 Gm. had been given. The oral dose varied considerably but was usually 0.5 to 1 Gm. every 4 hours. The indications for the discontinuance of oral therapy were evidence of toxicity or failure to convert the arrhythmia to a normal sinus rhythm within 24 hours.

The arrhythmias treated included: ventricular tachycardia, nodal tachycardia, paroxysmal auricular tachycardia, auricular flutter, auricular fibrillation, and multiple premature ventricular contractions. The drug was notably unsuccessful in the treatment of arrhythmias of auricular origin.

Although the intravenous route allowed more accurate evaluation of the effects of the drug the authors felt that because of the rarity of serious side effects from oral administration the latter was the route of choice. The most serious toxic effect was the development of hypotension. However, the authors also felt that intravenous procaine amide was less toxic than quinidine in therapeutic dosage administered by the same route.

BOOK REVIEWS

A German-English Dictionary for Chemists, Third Edition. By Austin M. Patterson, Antioch College. xviii + 541 pages. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y., 1950. Price $5.00.

This is the third edition of a well-known and highly regarded dictionary, used by chemists for many years. The vocabulary in this edition contains an estimated total of 59,000 terms; some of the larger additions have been in the fields of chemical technology, electronics, and warfare. Additional meanings are given for terms which were included in earlier editions. Nomenclature has been modernized and the book has been generally brought up to date.

LOUIS A. REBER

Physical Biochemistry. Henry B. Bull. Second Edition, 1951. 355 pages. John Wiley & Sons, Inc., New York, N. Y. $5.75.

In this edition, like the first, Dr. Bull has selected from the vast field of physical chemistry material which has unquestioned usefulness in solving and studying problems related to biological chemistry. The text has been carefully revised and considers in a concise manner the modern tools of the research biochemist, including light scatter, electrokinetic devices, tracer isotopes, the ultracentrifuge, X-rays, and viscometers. Comprehensive treatments are presented on reaction kinetics, surface activity, and naturally occurring polymers, as well as the fundamental concepts associated with atoms, molecules, ions, electromotive force, electrical conductance, acids and bases, oxidation-reduction, osmotic pressure, and diffusion.

This book is essentially a compact outline and as such is highly compressed. The beginner in the field will find it necessary to digest a little at a time and undertake extensive collateral reading, which is suggested by the well documented text.

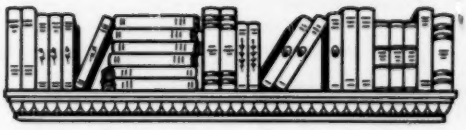
ERIC W. MARTIN

Colloidal Dispersions. By Earl K. Fischer, National Bureau of Standards. vii + 387 pages, incl. index. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y., 1950. Price $7.50.

An important feature of Dr. Fischer's book is the presentation of a considerable amount of practical information along with the development of the theoretical principles involved in the preparation and study of colloidal dispersions. It is concerned with the dispersion of solids in liquid media. A chapter on particle size gives an excellent discussion of the several available methods of measurement and a critical evaluation of their validity. Chapters on interfacial phenomena and wetting, flow properties of dispersions, and surface-active agents are included. The various types of milk useful in the formation of fine particles and in their dispersion are discussed. The book is concluded with a discussion of the "Flushing Process", the formation of dispersions by transfer of particles from one phase to another.

The book is up-to-date, the bibliography is good, and the field is throughly covered. It will be of greatest interest to those associated with the manufacture of pigments, paints, and inks and to others interested in the general problems of dispersing solid particles in liquid media.

LOUIS A. REBER



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